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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,844	09/10/1999	KATHERINE A. HIGH	10650/002002	3411

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,844	HIGH ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-9* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 30 December 2004 has been entered.

Claims 1-4 and 6-9 are presently pending and under examination.

Information Disclosure Statement

The IDS filed 30 December 2004 has been considered. The Koeberl *et al.* and Chen *et al.* publications were made of record in the IDS filed 8 June 2001 and the WO 96/15777 publication was made of record in the PTO-892 mailed 5 December 2000. Therefore, those documents have been lined through on the present IDS.

Notice To Comply With Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the

reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Upon reviewing the sequence listing and CRF it was discovered that the sequence listing filed 8 June 2001 does not match the CRF. Specifically, the organism identifier (field 213) for sequences 2-4 recites "human" in the CRF and "viral" in the sequence listing. Applicant must file a new sequence listing or CRF containing the proper organism identifier, along with the proper statements under Rule 1.821 (f) and (g).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Wilson *et al.* US Patent No. 5,866,552 (filed 6 September 1996; made of record in the Office Action mailed 5 December 2000).

Wilson *et al.* teaches a method for delivering and expressing a transgene delivered to an animal via a recombinant AAV virus vector (see especially, the fifth paragraph in column 1), which vectors comprise flanking AAV ITR's (see especially Figure 1 and the caption thereto). Wilson *et al.* further teaches a preferred embodiment wherein the method is used to treat hemophilia and involves introducing an AAV vector comprising a Factor IX gene into muscle

cells of an animal (see especially the seventh paragraph in column 1). The vector used in the method of Wilson *et al.* thus comprises two adeno-associated virus inverted terminal repeats and an isolated DNA encoding a Factor IX. Wilson *et al.* further teaches the use of an SV-40 poly adenylation signal which the skilled artisan would recognize as a transcription termination signal (see especially the paragraph bridging columns 5 and 6). Although Wilson *et al.* does not explicitly teach that the vector used in the method should comprise "accompanying 5' and 3'" untranslated sequence, this limitation, as it is understood, is inherent to the vector of Wilson *et al.* There is no definition of "accompanying 5' and 3' untranslated region" that would exclude any sequence expressed from the vector that is not translated from the 5' and 3' untranslated region of the claims. As described above, the vector of Wilson *et al.* comprises a polyadenylation signal, which would be 3' untranslated sequence, and all eukaryotic genes must comprise 5' untranslated sequence upon which the ribosome assembles in order for translation to occur. Thus, absent evidence to the contrary, the vector of Wilson *et al.* comprises "accompanying 5' and 3' sequence". Therefore, the composition of Wilson *et al.* anticipates the instant claim 1.

Furthermore, the vector comprised in a pharmaceutically acceptable carrier according to claim 6 would be inherent to a method involving administering into the muscle of an animal; Wilson *et al.* teaches the use of a CMV immediate early promoter/enhancer according to claim 7 (see especially the paragraph bridging columns 5-6); and Wilson teaches an SV40 termination signal according to claim 8 (*Id.*).

Claim 9 is directed to a kit comprising the virus of claim 1 and instructions for using the kit. Wilson *et al.* discloses a virus according to claim 1 and instructions for using the virus (*i.e.*,

administer to an animal). Thus, Wilson *et al.* discloses all of the elements of the kit of claim 9 and the claim is anticipated.

The AAV vector composition used in the method of Wilson *et al.* is the same as the vector claimed in the instant application; therefore, the claims are anticipated by Wilson *et al.*

Declaration under 37 CFR §1.131.

The evidence submitted 8 June 2001 is insufficient to establish a conception of the invention prior to the effective date of the Wilson *et al.* reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897).

The Declaration includes a single page from a laboratory notebook which includes a diagram of a plasmid labeled pSSV-F.IX intron. The diagram includes a 0.5 (presumably Kb) segment labeled CMV, 2.8 Kb segment labeled F.IX and a segment labeled $SV40^{+}$. Neither the diagram nor the other information contained in the notebook page includes all of the limitations set forth in claim 1. Most notably, there is no mention of AAV or AAV ITR's in the notebook page. Although some of the restriction digests refer to a "pAd" the abbreviation "Ad" is commonly understood to refer to adenovirus and not adeno-associated virus. Thus, the evidence provided does not adequately establish conception of an AAV virus vector comprising two ITR's. Furthermore, it is not clear from the evidence provided that the intron is a portion of intron 1 of a Factor IX gene or that the DNA encoding a factor IX comprises a mutation, that the

vector is comprised in a pharmaceutically acceptable carrier. In addition, there is no support for a promoter/regulatory sequence other than a CMV promoter and there are no instructions for using the virus. Thus, the limitations set forth in the dependent claims are clearly not supported by the evidence provided. Therefore, the evidence provided fails to establish conception of what is now claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson *et al.* US Patent No. 5,866,552, as applied to claim 1 above, in view of Wang *et al.* (1996) *Hum. Gene Ther.* 7:1743-1756 as evidenced by Kurachi *et al.* (1995) *J. Biol. Chem.* 270:5276-5281.

As described above, Wilson *et al.* teaches a method for delivering and expressing a transgene delivered to the muscle of an animal via a recombinant AAV vector, which vector comprises each of the limitations of the instant claim 1.

Wilson *et al.* does not teach that the construct should comprise a portion of intron 1 of a Factor IX gene from about 0.3 to 1.7 Kb according to claims 2 and 3 or a promoter/regulatory sequence that is a skeletal muscle actin promoter according to claim 7.

Wang *et al.* identifies a human factor IX minigene optimized for expression in muscle cells. In the paragraph bridging pages 1751-1752, Wang *et al.* teaches, "[o]n the basis of the results summarized above, the optimal basic structure of the hFIX expression vector to be used for production of hFIX by muscle-targeted gene transfer should contain βA [β-actin] promoter, Me2 or Me4, and the hFIX minigene." In particular, Wang *et al.* identifies the Xm1 minigene, which exhibited 10- to 14-fold higher expression than a cDNA construct, as the most effective Factor IX construct (see especially the paragraph bridging the left and right columns on page 1749). The Xm1 minigene, as disclosed in Kurachi *et al.*, comprises Factor IX 5' and 3' untranslated sequence and a truncated first intron of approximately 1.4 Kb (see especially Kurachi *et al.*, Figure 2 and the caption thereto and the first full paragraph in the right column on page 527).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the AAV vector of Wilson *et al.* to comprise the Factor IX minigene comprising a portion of the Factor IX gene first intron of about 0.3 to 1.7 Kb and a promoter/ regulatory sequence that is a skeletal muscle actin promoter according to the teachings of Wang *et al.*

Motivation to combine these teachings comes from the nature of the problem to be solved in the method of Wilson *et al.* (*i.e.*, obtaining sufficient expression of Factor IX from muscle cells to provide therapeutic effect in the treatment of hemophilia) and the teachings of Wang *et al.* which demonstrate that the Xm1 minigene is optimal for expression of Factor IX in muscle cells (see *supra*).

Thus, the teachings of Wilson *et al.* and Wang *et al.* provide both instruction in how to make a pharmaceutical composition comprising each of the elements of the virus of the instant claims and motivation to make the virus. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings because Wilson *et al.* demonstrate high level transduction of muscle fibers using the AAV vector (see especially Example 2) and Wang *et al.* demonstrates expression of the βA-Xm1 minigene in skeletal muscle cells (see especially Figure 7 and the caption thereto).

For these reasons, the limitations of claims 1-3 and 7, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103 as obvious over the art.

Allowable Subject Matter

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

PRIMARY EXAMINER

Application No. 09/393844

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☒ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing" or

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.